EXHIBIT A

FIFTEENTH EDITION

THE MERCK MANUAL

OF

DIAGNOSIS AND THERAPY

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FOREWORD

THE MERCK MANUAL first appeared in 1899 as a slender 262-page text titled MERCK'S MANUAL OF THE MATERIA MEDICA. It was expressly designed to meet the needs of general practitioners in selecting medications, noting that "memory is treacherous" and even the most thoroughly informed physician needs a reminder "to make him at once master of the situation and enable him to prescribe exactly what his judgment tells him is needed for the occasion." It was well received and, by the 6th Edition (1934), THE MERCK MANUAL had become highly valued by medical students and house staff also; by the end of World War II the pocket-sized manual was an established favorite ready-reference. Today THE MANUAL is the most widely used medical text in the world. While the book has grown to about 2500 pages, its primary purpose remains the same—to provide useful information to practicing physicians, medical students, interns, residents, and other health professionals.

Fewer physicians now attempt to manage the whole range of medical disorders that can occur in infants, children, and adults, but those who do must have available a broad spectrum of current and accurate information. The specialist requires precise information about subjects outside his area of expertise. All physicians need more and more information for study and examination purposes as well as for patient care. THE MERCK MANUAL continues to try to meet these needs, excluding only details of surgical procedures.

Precisely how do we attempt to meet these needs? First, from a disease orientation, THE MANUAL covers all but the most obscure disorders of mankind, not only those that a general internist might expect to encounter, but also problems of pregnancy and delivery, the more common and serious disorders of neonates, infants, and children, and many special situations. Disorders are mainly organized according to the organ systems primarily affected, on the basis of their etiology (as with most of the infectious diseases and disorders due to physical agents), or on the basis of disciplines (eg, gynecology, obstetrics, pediatrics, genetics, psychiatry). In addition, THE MANUAL contains information for special circumstances, such as radiation reactions and injuries, problems encountered in deep-sea diving, or dental emergencies. The entire book is updated for each new edition, and new subjects continue to be added, such as discussions of diagnostic and therapeutic procedures in gastroenterology, acquired immunodeficiency syndrome (AIDS), reproductive endocrinology, oncology, the management of severe and chronic pain, the value of hyperbaric O_2 therapy, and special considerations in drug treatment of infants and children. This edition has 114 pages (approximately 5%) more text than the preceding edition. We therefore urge you to check the Index whenever you require information, even on unusual subjects or those not commonly found in other texts.

A completely disease-oriented compendium, however, would have serious limitations. Since patients usually present with complaints or concerns that must be meticulously described, sorted, and deciphered, many chapters are devoted to discussions of symptoms and signs and how to elicit the historical and physical data required for diagnosis. Common clinical procedures and laboratory tests used as diagnostic and management aids are described with emphasis on their indications, contraindications, and possible complications. New and sophisticated laboratory and technologic procedures are also described, with comments on their uses, interpretations, and limitations.

Current therapy is presented for each disorder and supplemented with a separate section on clinical pharmacology that describes general principles, new ad-

vances (eg, the role of drug receptors, plasma concentration monitoring), details of pharmacologic groups and specific agents, and even a discussion on the use of placebos. The use of complex equipment (eg, respirators) is also described. Prophylaxis is emphasized wherever possible. Finally, reference guides are provided for checking normal values, calculating dosages, and converting weights, measures, and volumes to metric equivalents.

Can so many subjects be covered adequately in a single book? You, the reader, must make the ultimate judgment, but we believe the answer is in the affirmative. This edition required a concerted effort by many people, beginning with an internal analysis and critique of the previous edition, even though it enjoyed highly favorable reviews and outstanding reader acceptance. Sections of that book were then sent to outside experts, who had had nothing to do with its preparation, to solicit their most candid criticism. Published reviews and letters received from readers were analyzed. Next, the Editorial Board met to compare reviews and critiques and to plan this 15th Edition. Distinguished special consultants were enlisted to provide additional expertise. Then, 269 authors with outstanding qualifications, experience, and knowledge were engaged. Their manuscripts were edited repeatedly in-house to retain every valuable morsel of knowledge while eliminating sometimes elegant, but unneeded, words. Each manuscript was then reviewed by a member of the Editorial Board or a consultant. In many cases, additional special reviewers were invited to comment. Every mention of a drug and its dosage was reviewed by a separate outside consultant. The objectives of all these reviews were to ensure adequate and relevant coverage of each subject, accuracy, and simple and clean exposition. The authors then reworked, modified, and polished their manuscripts. Almost all of the manuscripts were revised at least 6 times; 15 to 20 revisions were not uncommon. We believe that no other medical text undergoes as many reviews and revisions as THE MERCK MANUAL.

Owing to the extensive subject matter covered and a successful tradition, the style and organization of THE MANUAL have some unique characteristics. Readers are urged to spend a few minutes reviewing the Guide for Readers (p. viii), the Table of Contents *at the beginning of each section,* and the Index (p. 2577). Scrutiny of the arrangement of subject headings within each section, of internal headings within a subject discussion, and of boldfaced terms in the text will reveal a pattern of outlining intended to aid study of the text.

The foregoing is a simplified review of the complex, arduous, and rewarding 5-year enterprise that culminates in the presentation of this 15th Edition of THE MERCK MANUAL. The members of the Editorial Board, special consultants, contributing authors, and in-house editorial staff and their affiliations are listed on the pages that follow. They deserve a degree of gratitude that cannot be adequately expressed here, but we know they will feel sufficiently rewarded if their efforts serve your needs.

We hope this edition of THE MERCK MANUAL will be a welcome aid to you, our readers—compatible with your needs and worthy of frequent use. Suggestions for improvements will be warmly welcomed and carefully considered.

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CONTENTS

Prognosis, Prophylaxis, and Treatment

Despite the severity of the symptoms during acute attacks, most patients are remarkably free of illness between attacks. Widespread use of colchicine has dramatically reduced the incidence of amyloidosis. When it does occur, the prognosis is much poorer; eg, in the past, about 25% of FMF patients in Israel were known to have amyloidosis, and it was usually fatal.

Colchicine aborts attacks and reduces recurrence. Its mechanism of action is unknown; possibly it prevents normal cellular response to inflammation. For prophylaxis, the dosage is 0.6 mg orally tid, and is reduced to bid if GI side effects develop. For acute attacks, the dosage is 0.6 mg/h orally for 4 h, then q 2 h for 4 h, then q 12 h for 48 h. Narcotics should be *avoided*, since drug addiction or habituation is a possible and serious complication.

§2. IMMUNOLOGY; ALLERGIC DISORDERS

16. INTRODUCTION

The science of immunology began with an attempt to understand resistance to infection, which was initially thought to be the only function of the immune system. Its relationship to hypersensitivity (allergy) was recognized early in this century and led to elucidation of the general biologic functions of the immune system, including a role in

increased gradually until the bag is empty after 20 to 30 min. This is then repeated with concentrations of 1,000 and 10,000 u./mL, followed by the full therapeutic dose. If any allergic symptoms develop, the flow rate should be slowed, and the patient given appropriate drug treatment (see Anaphylaxis, above). IV desensitization is safer than s.c. or IM desensitization because not only the amount but also the rate of administration of the drug is under control. **Oral desensitization** also is safe and effective. The first dose is 100 u. (or μg); the following doses are doubled every 15 min, and symptoms are relieved with suitable anti-anaphylactic drugs if they occur. Whichever route is used, the starting dose should be a thousandfold lower if the prick test for penicillin is positive, but this practically never happens.

SERUM SICKNESS

An allergic reaction usually appearing 7 to 12 days after administration of a foreign serum or certain drugs, characterized by fever, arthralgias, skin rash, and lymphadenopathy.

Etiology

The most common cause of serum sickness is not serum, but pencillin and related drugs (see DRUG HYPERSENSITIVITY, above). Reactions from horse serum antitoxins occur in at least 5% of persons given the serum for the first time. Serum reactions have become infrequent with current active-immunization programs and antibiotics, and with the development of human immune sera for tetanus and rabies. However, horse antiserum is still used in managing diphtheria, botulism, and venomous snake and spider bites; and anti-lymphocyte or -thymocyte serum from horses and other species is used to suppress immune reactions to transplanted organs.

Injected serum is slowly excreted, so that it remains in the circulation long enough to simulate production of specific IgG antibodies that form soluble complexes with the antigen to cause an immune complex (Type III) reaction; IgE antibodies and consequently an IgE-mediated reaction also are produced. (See Ch. 20 for a discussion of the immunologic mechanisms.) Little evidence exists for an IgG immune complex mechanism in serum-sickness-type reactions caused by small-molecular-weight drugs.

Symptoms and Signs

Onset is usually several days after injection of the serum or drug but may be much sooner than the usual 7 days if the patient has been exposed previously (**anaphylaxis** or **accelerated serum sickness**). Urticaria is the usual skin manifestation. Less frequently, the rash may be multiform or morbilliform; rarely, it is scarlatiniform or purpuric. Most patients have polyarthritis or periarticular edema. Temporomandibular arthritis may be severe, and has been confused with tetanus. When fever occurs, it is mild and lasts for only 1 or 2 days. Adenopathy develops in the region draining the injection site and may become generalized. Splenomegaly is sometimes present. Occasionally, abdominal pain and diarrhea may accompany other symptoms. Myocarditis may develop but is rare. Peripheral neuritis is the only complication that may cause irreversible injury. Surprisingly, glomerulonephritis, so prominent in experimental serum sickness in animals, is rarely a problem.

Prophylaxis in Using Animal Serum to Avoid Anaphylaxis

Before giving any animal serum or animal serum product, the patient should be asked whether he has ever received serum before and whether he has a history of asthma, hay fever, urticaria, or other allergic symptoms—particularly on exposure to horses. A positive history calls for special caution to avoid acute anaphylactic reactions.

Regardless of history, any person about to receive a foreign serum *must be tested first*. Some written instructions still call for an intracutaneous test using 0.1 mL of a 1:10 dilution, but this procedure is unsatisfactory and may be dangerous: It produces many false-positive reactions and is likely to produce a generalized reaction in an allergic patient. A patient who is not atopic and who has not received horse serum previously should first be given a **prick test** with a 1:10 dilution; if this is negative, 0.02 mL of a 1:10 dilution is injected intracutaneously. A wheal more than 0.5 cm in diameter will develop within 15 min if the patient is sensitive. All patients who may have received serum previously (*whether or not they reacted*) and those with a suspected allergic history should be tested first with a 1:1000 dilution. Negative skin test results make anaphylaxis (IgE-mediated reaction) unlikely but do not predict the incidence of subsequent serum sickness.

Desensitization to foreign serum: If the skin test is positive, the risk of anaphylaxis is high. If serum treatment is essential, then desensitization is necessary first. Skin tests, using weaker concentrations prepared by serial dilution, are performed to determine the proper starting dose for desensitization, which is at the concentration that gave a weak or negative reaction. One-tenth mL of this injected s.c. or slowly IV; although not the standard method, the IV approach, as with penicillin desensitization, gives the physician control over both the concentration and rate of delivery. If no reaction occurs in 15 min, the dose is doubled every 15 min until 1 mL of undiluted serum is given. This dose is repeated IM, and if no reaction occurs in another 15 min, the full dose can be given. If a patient does react, it may still be possible to proceed cautiously by cutting back the dose, treating with an antihistamine and glucocorticoid, given as for acute urticaria, and then increasing with smaller increments.

Whenever desensitization is to be carried out, O_2, epinephrine, and resuscitation equipment must be at hand to initiate prompt treatment of anaphylaxis.

Treatment

Since the disease is self-limited, treatment of serum sickness is usually restricted to relief of symptoms. Pruritus is treated with an antihistamine as for acute urticaria; arthralgias, with salicylates (aspirin 0.6 to 1.5 gm orally q 4 h). If these are not adequate, prednisone 30 mg/day orally is almost always effective; the dose is gradually reduced to zero after symptoms have been relieved. Early, intensive glucocorticoid treatment is necessary if the rare complications of peripheral neuritis or myocarditis develop.

AUTOIMMUNE DISORDERS

Disorders in which the immune system produces autoantibodies to an endogenous antigen, with consequent injury to tissues.

Considered here are the pathogenetic immunologic mechanisms underlying autoimmune diseases (see also TABLE 21–1). Clinical aspects of the specific disorders are presented elsewhere in THE MANUAL.

Development of the Autoimmune Response

Although precise details of the autoimmune response are incompletely understood, the outcome of antigenic stimulation, whether antibody formation or activated T cells or tolerance, seems to depend on the same factors with autoantigen as with exogenous antigen. Four possible mechanisms for developing an immune response to autoantigens are recognized:

1. Hidden or sequestered antigens (eg, intracellular substances) may not be recognized as "self"; if released into the circulation they may induce an immune response. This occurs in sympathetic ophthalmia with the traumatic release of an antigen normally sequestered within the eye. Autoantibody alone may not produce disease because it cannot combine with the sequestered antigen. For example, antibodies to sperm and

TABLE 21–1. PUTATIVE AUTOIMMUNE DISORDERS

	Disorder	Mechanism or Evidence
Highly Probable	Hashimoto's thyroiditis	Cell-mediated and humoral thyroid cytotoxicity
	Systemic lupus erythematosus	Circulating and locally generated immune complexes
	Goodpasture's syndrome	Anti-basement membrane antibody
	Pemphigus	Epidermal acantholytic antibody
	Receptor autoimmunity	
	Graves' disease	TSH receptor antibody (stimulatory)
	Myasthenia gravis	Acetylcholine receptor antibody
	Insulin resistance	Insulin receptor antibody
	Autoimmune hemolytic anemia	Phagocytosis of antibody-sensitized erythrocytes
	Autoimmune thrombocytopenic purpura	Phagocytosis of antibody-sensitized platelets
Probable	Rheumatoid arthritis	Immune complexes in joints
	Progressive systemic sclerosis	Nucleolar and other nuclear antibodies
	Mixed connective tissue disease	Antibody to extractable nuclear antigen (ribonucleoprotein)
	Polymyositis	Non-histone ANA*
	Pernicious anemia	Anti-parietal cell, microsomes, and intrinsic factor antibodies
	Idiopathic Addison's disease	Humoral and (?) cell-mediated adrenal cytotoxicity
	Infertility (some cases)	Antispermatozoal antibodies
	Glomerulonephritis	Glomerular basement membrane antibody, or immune complexes
	Bullous pemphigoid	IgG and complement in basement membrane
	Sjögren's syndrome	Multiple tissue antibodies, a specific non-histone ANA (SS-B)
	Diabetes mellitus (some)	Cell-mediated and humoral islet cell antibodies
	Adrenergic drug resistance (some asthmatics)	β-adrenergic receptor antibody
Possible	Chronic active hepatitis	Smooth muscle antibody
	Primary biliary cirrhosis	Mitochondrial antibody
	Other endocrine gland failure	Specific tissue antibodies in some cases
	Vitiligo	Melanocyte antibody
	Vasculitis	Some cases: immunoglobulin and complement in vessel walls, low serum complement
	Post-myocardial infarction, cardiotomy syndrome	Myocardial antibody
	Urticaria, atopic dermatitis, asthma (some cases)	IgG and IgM antibodies to IgE
	Many other inflammatory, granulomatous, degenerative, and atrophic disorders	No reasonable alternative explanation

* ANA = Antinuclear antibody.

heart muscle antigens are blocked by the basement membrane of the seminiferous tubules and myocardial cell membrane, respectively. Immunologically active T cells, however, may not have such restrictions and would be more effective in producing injury.

2. The "self" antigens may become immunogenic because of chemical, physical, or biologic alteration. Certain chemicals couple with body proteins and render them immunogenic, as seen in contact dermatitis. Drugs can produce several autoimmune reactions (see DRUG HYPERSENSITIVITY, above). Photosensitivity exemplifies physically induced autoallergy: ultraviolet light alters skin protein, to which the patient becomes allergic. Biologically altered antigens are seen in New Zealand mice that develop autoallergic disease resembling SLE when persistently infected with an RNA virus known to combine with host tissues, altering them sufficiently to induce antibody.

3. Foreign antigen may induce an immune response that cross-reacts with normal "self" antigen. Examples are the cross-reaction that occurs between streptococcal M protein and human heart muscle, and the encephalitis that can follow rabies vaccination in which an autoimmune cross-reaction probably is initiated by animal brain tissue in the vaccine.

4. Autoantibody production may be a result of mutational change in immunocompetent cells. This may explain the monoclonal autoantibodies seen occasionally in patients with lymphoma.

Finally, autoimmune phenomena may be epiphenomena, and the primary pathogenesis the result of an immune response to an obscure antigen; eg, a virus.

Probably the autoimmune reaction is normally held in check by the action of a population of specific suppressor T cells. Any of the above processes could lead to, or be associated with, a suppressor T cell defect. Perhaps a perturbation in the regulation of antibody activity by anti-idiotype antibodies (antibodies to the antigen combining site of other antibodies) may play a role.

The role of other complex mechanisms demonstrable experimentally still needs clarification. For example, adjuvants such as alum or bacterial endotoxin, while not antigenic themselves, enhance the antigenicity of other substances. Freund's complete adjuvant, an emulsion of antigen in mineral oil with heat-killed mycobacteria, is usually required in order to produce autoimmunity in experimental animals.

Genetic factors play a role in autoimmune disorders. Relatives of patients with autoimmune disorders often show a high incidence of the same type of autoantibodies, and the incidence of autoimmune disease is higher in identical than in fraternal twins. Women are more often affected than men. The genetic contribution appears to be one of predisposition. In a predisposed population a number of environmental factors could provoke disease; eg, in SLE these might be latent virus infection, drugs, or tissue injury such as occurs with ultraviolet light exposure. This situation would be analogous to the development of hemolytic anemia as a consequence of environmental factors in persons with G6PD deficiency, a predisposing genetically determined biochemical abnormality.

Pathogenesis

The pathogenetic mechanisms of autoimmune reactions are, in many cases, better understood than the way in which autoimmune antibodies develop. In some autoimmune hemolytic anemias, the RBCs become coated with cytotoxic (Type II) autoantibody; the complement system responds to these antibody-coated cells just as it does to similarly coated foreign particles, and the interaction of complement with the antibody complexed to the cell surface antigen leads to RBC phagocytosis or cytolysis.

Autoimmune renal injury can occur as the result of either an antibody-mediated (Type II) or immune complex (Type III) reaction. The antibody-mediated reaction occurs in Goodpasture's syndrome, in which lung and renal disease is associated with the presence of an anti-basement membrane antibody (see Ch. 44). The best-known example of autoimmune injury associated with soluble antigen-antibody complexes (immune complexes) is the nephritis associated with SLE (see in Chs. 110 and 149 and below). Another example is a form of membranous glomerulonephritis that is associated with an immune complex containing renal tubular antigen. Although it is possible

that poststreptococcal glomerulonephritis could be due in part to streptococcus-induced cross-reacting antibodies, there is as yet no proof of this.

A variety of autoantibodies are produced in **SLE** and other systemic (as opposed to organ-specific) autoimmune diseases. Antibodies to formed elements in the blood account for autoimmune hemolytic anemia (see in Ch. 96), thrombocytopenia, and possibly leukopenia; anticoagulant antibodies may cause bleeding problems. Antibodies to nuclear material result in deposition of antigen-antibody complexes, not only in glomeruli, but also in vascular tissues and in skin at the dermal-epidermal junction. Synovial deposition of aggregated IgG-rheumatoid factor **(RF)**-complement complexes occurs in **RA. RF** is usually an IgM globulin (occasionally IgG or IgA) with specificity for a receptor on the constant region of the heavy chain of autologous IgG. The IgG-RF-complement aggregates can also be found within neutrophils, where they cause the release of lysosomal enzymes that contribute to the inflammatory joint reaction. Plasma cells are also present in large numbers within the joint, and may synthesize anti-IgG antibodies. T cells and lymphokines are also found in rheumatoid joints and may contribute to the inflammatory process. The process that sets off the immunologic events is unknown; it could be a bacterial or viral infection. In SLE the low serum complement level reflects the widespread immunologic reactions taking place; in RA, by contrast, serum complement is normal but intrasynovial complement levels are low.

In **pernicious anemia,** autoantibodies capable of neutralizing intrinsic factor are found in the GI lumen. Autoantibodies against the microsomal fraction of gastric mucosal cells are even more common. It is postulated that a cell-mediated autoimmune attack against the parietal cells results in the atrophic gastritis that, in turn, reduces the production of intrinsic factor but still allows absorption of sufficient vitamin B_{12} to prevent the megaloblastic anemia. If autoantibodies to intrinsic factor should also develop in the GI lumen, however, B_{12} absorption will cease and pernicious anemia will develop.

Hashimoto's thyroiditis is associated with autoantibodies to thyroglobulin, the microsomes of thyroid epithelial cells, a thyroid cell-surface antigen, and a second colloid antigen. Tissue injury and eventual myxedema may be mediated both by the cytotoxicity of the microsomal antibody and by the activity of specifically committed T cells. Low-titered antibodies are also found in patients with primary myxedema, suggesting that it is the end result of unrecognized autoimmune thyroiditis. An autoimmune reaction is also involved in thyrotoxicosis **(Graves' disease),** and about 10% of patients eventually develop myxedema spontaneously; many more do so after ablative therapy. Other antibodies, unique to Graves' disease, are called thyroid-stimulating antibodies. They react with thyroid-stimulating hormone **(TSH)** receptors in the gland and have the same effect on thyroid cell function that TSH normally has.

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22. TRANSPLANTATION

The transfer of living tissues or cells from one individual to another, with the objective of maintaining the functional integrity of the transplanted tissue in the recipient.

GENERAL CONSIDERATIONS

Despite surgical technics making transplantation of almost any tissue feasible, the clinical use of transplantation to remedy disease is still limited for many organ systems. The greatest obstacle is the **rejection reaction,** which generally destroys the tissue shortly after transplantation (except in special circumstances, such as most corneal and cartilage grafts, or transplants between identical twins). Nevertheless, with improved understanding of immune mechanisms and methods for preventing rejection, organ transplantation now saves many patients with otherwise fatal disease. In addition, although the cost of organ transplantation is high, it is a curative treatment for end-stage organ failure. The cost of alternative noncurative terminal care of patients with end-stage organ failure can be exorbitant.

Transplants are categorized by the site of transplantation and by the genetic relationship between donor and recipient. A tissue or organ graft is **orthotopic** if it is transferred to an anatomically normal recipient site—as in a heart transplant. If the transplant is to an anatomically abnormal site, it is **heterotopic**—as in the transplantation of a kidney into the iliac fossa of the recipient. An **autograft** is a transfer of tissue from one location to another in the same individual (eg, bone grafting for fracture stabilization). An **isograft** is a graft between identical twins; an **allograft (homograft)** is one between genetically dissimilar members of the same species. **Xenografts (heterografts)** are transplants between members of different species.

The only xenografts now performed are with fixed, nonviable material such as porcine heart valves. With rare exceptions clinical transplants are thus allografts from either living relatives or cadaveric donors. The use of living donors is only appropriate in kidney transplantation, and even for kidneys the need for organs far exceeds the number available from relatives of patients with chronic renal failure. Use of cadaveric organs has become more prevalent as the concept of brain death has gained acceptance. As the demand for cadaveric organs has increased, procedures for procuring multiple organs from a single donor have become common. Kidneys, liver (or pancreas), heart (or heart/lungs), bones, skin, and corneas can now routinely be procured at a single operative procedure.

IMMUNOBIOLOGIC PRINCIPLES

Allografts may be rejected through either a cell-mediated or a humoral immune reaction of the recipient against **transplantation (histocompatibility) antigens** present on the donor's cell membranes. The strongest antigens are governed by a complex of genetic loci and are termed **HLA** (see below); together with the major blood group **(ABO)** antigens, they are the chief transplantation antigens presently detectable in man. Because transplantation antigens can be identified by their effects in vitro, tissue typing (see TISSUE COMPATIBILITY, below) is possible.

The **lymphocyte (cell)-mediated immune reaction** against transplantation antigens (ie, the **host-vs.-graft reaction [HVGR]**) is the principal mechanism of **acute rejection.** A delayed hypersensitivity response similar to the tuberculin reaction, HVGR causes graft destruction days to months after transplantation and is characterized histologically by mononuclear cellular infiltration of the allograft, with varying degrees of hemorrhage and edema. Usually, vascular integrity is maintained; thus, cell-mediated rejection may be reversed in many cases by intensifying immunosuppressive therapy. After successful reversal of an acute episode, histologic examination shows that severely damaged elements of the graft have healed by fibrosis and that the remainder of the graft appears to be normal. After resolution of acute rejection, the allograft will commonly survive for prolonged periods, even though the immunosuppressive drug dosages have been reduced to very low levels. This process of "graft adaptation" is most likely explained by development of donor-specific suppression of the recipient's immune response.

Late graft deterioration occurs occasionally in immunosuppressed patients. This chronic type of rejection is often insidious but relentless in progression despite increased immunosuppressive measures. The pathologic picture differs from that of acute rejection. The vascular endothelium is primarily involved, with extensive proliferation that gradually occludes the vessel lumen, resulting in ischemia and fibrosis of the graft.